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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,627	02/26/2004	Howard Kaufman	19240.461-US2	7662

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EXAMINER	
SINGH, ANOOP KUMAR	

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
05/13/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/789,627	KAUFMAN ET AL.	
	Examiner	Art Unit	
	ANOOP SINGH	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-7,11-15,18-21,23-27,33,35-37,42-44,48-52,54-56,60,65 and 66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-7,11-15,18-21,23-27,33,35-37,42-44,48-52,54-56,60,65 and 66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/9/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants amendments to the claims and arguments filed 02/18/2009 have been received and entered. Claims 2-4, 8-10, 16-17, 22, 28-32, 34, 38-41, 45-47, 53, 57-59, 61-64 have been cancelled, while claims 1, 7, 26-27, 33, 35, 37, 43-44, 56 60 and 65 have been amended. Applicants have also added claim 66 generally directed to elected invention.

Election/Restrictions

Applicant's election of claims 1-29, 33-61 and 65 (group V) drawn to a composition for delivering a therapeutic agent to a target cell, comprising a microorganism that has on its cell surface an exogenous molecule that binds the target cell and a therapeutic agent wherein the therapeutic agent is a nucleic acid and a method for using said composition in treating neoplasia in the reply filed on April 9, 2007 was acknowledged. Applicants also elected the following species: colon cancer cell, and carcinoembryonic antigen (CEA). In response to additional restriction requirement mailed on 1/28/2008, applicants have elected nucleic acid encoding a polypeptide that is immuno enhancing factor.

Claims 1, 5-7, 11-15, 18-21, 23-27, 33, 35-37, 42-44, 48-52, 54-56, 60, 65 and 66 are directed to an attenuated Salmonella microorganism that displays CEA antibody on its surface that binds the target cell and a therapeutic agent wherein the therapeutic agent is a nucleic acid and method of treating neoplasia using said microorganism is under examination.

Claims 1, 5-7, 11-15, 18-21, 23-27, 33, 35-37, 42-44, 48-52, 54-56, 60, 65 and 66 are under consideration.

Withdrawn- Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33, 35-37, 42-44, 48-52, 54-56, 60, 65 were rejected under 35 U.S.C. 112, first paragraph. Applicants' amendments to the base claim is persuasive and instant specification enables one skilled in the art to make and/or use the invention directed to a method of targeting neoplastic cells in a subject comprising; (a) administering directly to the neoplastic cells of a solid tumor in a subject an attenuated Salmonella microorganism that has, on its surface, at least one antibody or fragment thereof that binds to a neoplasm- specific antigen on the surface of a neoplastic cell of a solid tumor in the subject: wherein neoplastic cell is a carcinoembryonic-antigen- (CEA)-expressing cell; (b) binding of the attenuated Salmonella to the neoplastic cell; and (c) infecting the neoplastic cell. Applicants amendments to the claims and arguments filed 10/9/2008 have been persuasive. Therefore, rejection is hereby withdrawn.

Maintained-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 5-7, 11-15, 18-21, 23-27, 29, 33, 35-37, 42-44, 48-52, 54-56, 60, 65 remain rejected under 35 U.S.C. 103(a) and newly added claim 66 is also rejected under 35 U.S.C. 103(a) as being unpatentable over Bermudes et al (US patent application no. 20050249706, dated 11/10/2005, effective filing date 10/4/1999) or Szalay et al (US patent application no 20050069491, dated 3/31/2005, effective filing

date 7/31/2002), Francisco et al (Proc Natl Acad Sci U S A. 1993; 90(22): 10444-8) and Wu et al. (Immunotechnology,1996, 2:21-36).

Applicants' arguments filed October 9, 2008 have been fully considered but are not persuasive. Applicants argue that the presently claimed invention is directed to a composition for delivering an agent to a neoplastic cell of a solid tumor expressing a neoplasm-specific antigen, wherein the composition comprises an agent and an attenuated *Salmonella* microorganism that has an antibody or fragment thereof on its cell surface that binds to a neoplasm-specific antigen on the surface of a neoplastic cell of a solid tumor. Applicants describe the teaching of each reference individually (see page 4 of the argument) and then assert that the skilled artisan would not have had a reasonable expectation of success in obtaining the claimed composition. Applicants argue that a protein must express at sufficient levels to elicit an effect; a protein must not be degraded by the organism's intrinsic cellular machinery; a protein must be folded properly and be stable; the protein must be adhered to the cell surface; once expressed on the cell surface of a *Salmonella* organism, the protein must be an active protein. Furthermore, one of ordinary skill in the art would have had no reasonable expectation that an antibody would be expressed on the surface of an organism, and subsequently would efficiently target a solid tumor, as alleged by the Examiner. Applicants cite Phizicky and Fields (Exhibit C; *Microbiological Reviews* (1995) 59(1): 94-123) and Van Criekinge and Beyaert (Exhibit B; see p. 3, 1st paragraph; *Biol Proced Online* (1999) 2(1): 1-38) to argue that use of bacterial host may preclude the correct folding of some protein. Applicants assert that it would not be predictable for the reasons discussed above; thus, one of ordinary skill in the art would not have reasonably expected success in making and using the claimed composition of the invention. Applicants also cites Theriot's paper (Exhibit D; *Ann Rev. Cell Dev Biol* (1995), 11 :213-39) to show the differences between different types of pathogenic bacteria.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It is relevant to point that the claims are directed to a composition comprising an attenuated Salmonella microorganism that has on its surface at least one antibody that binds to CEA (elected specie) on the surface of a neoplastic cell and an agent. Subsequent claims limit the strain of microorganism and type of an antibody. Claims are also directed to a method of administering to a subject having caner the composition of the invention. As previously indicated, contrary to applicants' assertion that teaching of cited art being unpredictable, it is noted that, Bermudes et al/ Szalay et al both teach an attenuated strain of *Salmonella typhimurium* (VNP 200009 see figure 2) that may comprise effector molecules which are encoded by a plasmid or transfectable nucleic acid, wherein more than one effector molecule (e.g., primary or secondary) is expressed in an attenuated tumor-targeted bacteria (see para. 60 of the published application) in the treatment of variety of cancer including colon cancer (see para. 71). It is noted that composition disclosed by comprises an attenuated Salmonella microorganism and an secondary effector molecule that includes therapeutic agent comprising a nucleic acid encoding immuno modulating protein such as Interleukin-1, 2, 4 (see para. 201) (limitation of claim 1, 25-27, 33, 26, 60). It is also disclosed that compositions and methods of the invention is not limited to Salmonella but may encompass any other bacterium including Escherichia coli, Salmonella spp and Shigella spp (see para.147). These assertions clearly show that these different strains of gram negative bacteria could be used to target tumor cells. Further, Bermudes et al teach delivering attenuated tumor-targeted strain of Salmonella VNP20009 carrying an and plasmid which expresses a hexahistidine-endostatin fusion protein demonstrating the inhibitory effect of the hexahistidine-endostatin expressing

attenuated tumor targeted Salmonella on the growth of DLD1 human colon carcinoma (see example 13, para. 380-388). Furthermore, Bermudes et al embraced the potential of delivering transgene under the control of CEA promoter (para. 271) and exemplified a method of delivering genetically modified attenuated Salmonella VNP20009 that is specifically retained in the tumor and not in liver suggesting specific binding and infection of microorganism to cancer cells (see example 16) meeting the limitation of claims 33 and 65). Furthermore, Bermudes et al disclosed a number of therapeutic agents could be delivered to the tumor cells including a nucleic acid encoding immuno modulating protein such as Interleukin-1, 2, 4 (see para. 201) meeting the limitation of claim 60. Bermudes et al also teach administering the compositions by any convenient route including infusion or bolus injection, oral, systemic or subcutaneous (see para. 297-298) (limitation of claim 66). The genetically modified *Salmonella typhimurium* disclosed by Bermudes et al and those embraced by the instant claims appear to be structurally same. Similarly, Szalay et al also disclose availability of another attenuated strain of *Salmonella typhimurium* (SL7207 see para. 96) that may be genetically modified to target variety of cancer including bladder, breast, prostate tumors, brain and colon (see para. 68 and figure 9-12). Although, Bermudes/Szalay et al embraced the potential of attenuated Salmonella VNP20009 or Shigella to target variety of tumor including colon cancer, Bermudes /Szalay differed from claimed invention by not disclosing expressing an antibody or a neoplasm specific antigen on the surface of the microorganism.

However, prior to instant invention art provided adequate guidance with respect to displaying a functional scFv antibody fragment to the outer surface of bacterium. This is supplied by the reference of Francisco et al who teach a method for displaying a functional scFv antibody fragment to the outer surface of E. coli microorganism that is capable of binding to an antigen with high affinity that also transformed with a construct comprising chloramphenicol-resistance gene (see

material and methods page 10444, col. 2, para 1 and 10445, col. 2, para. 2 and 3). Wu provided guidance with respect to the sequences of anti-CEA diabody T84.66VL-GS8 linker-VH (T84.66-GS8) or scFv T-84.66VL-GS18 linker-VH (T84.66-GS18), wherein antibody is a mammalian antibody or chimeric humanized antibody (see page 23, col. 1, last para. bridging to col. 2). Wu et al reported producing stable dimers of anti-CEA scFv that have excellent tumor targeting properties: substantial and persistent tumor uptake coupled with rapid clearance from blood and normal tissues (see Figure 7, table 3 and page 35, col. 1, para. 2). Accordingly, in view of the teachings of Bermudes et al/ Szalay, Francisco and Wu, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention to modify the genetically modified attenuated strain of *Salmonella typhimurium* (VNP 200009 or SL7207) or Shigella to display a functional scFv antibody fragment such as CEA antibody on the outer surface that targets CEA antigen present on certain tumor (colon). With respect to applicants' arguments pertaining to bacterial host may preclude the correct folding of some protein, it is noted that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See In re O'Farrell, 7 USPQ2d 1673 (CAFC 1988). Additionally, claims as recited are broad and do not require any specific embodiment or level of activity.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., a protein must express at sufficient levels to elicit an effect) are not recited in any of the rejected composition claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). It is noted that as recited instant claims do not require protein expression to any specific level, nor does composition claims requires any therapeutic effect as argued by the applicants.

With respect to applicants' argument of correct folding of protein and other related issue, it is noted that at the time of filing of this application there were several strategy by which one of ordinary skill in the art would have displayed antibody on the surface of a bacterium. It is noted that art teach that use of Lpp-OmpA fusion vehicle for bacterial surface display. Specifically, Francisco et al teach expressing a single chain Fv antibody fragment on the surface of *E.coli* by fusing it to an Lpp-OmpA hybrid that was known to direct heterologous proteins to the cell surface. In fact, Francisco et al teach a method of using FACS based method to enrich scFv-producing cells (see abstract). Additionally, with respect to Phizicky and Fields (Exhibit C; Microbiological Reviews (1995) 59(1): 94-123) cited by applicants to show disadvantage of phage display, it is noted that cited prior arts do not suggest these limitations in displaying CEA on the surface of the bacterium using Lpp-OmpA fusion vehicle. Applicants have not provided any additional evidence to show displaying CEA antibody using Lpp-OmpA system is not enabling for other gram negative bacteria such as Shigrlla or Salmonella. In absence of the evidence to the contrary, it is reasonable to state that each of the claimed elements found within the scope and content of prior art, one of ordinary skill in the art could have combined the different element using known method to produce claimed composition with reasonable expectation of achieving predictable results . It is further noted that, contrary to applicants' assertion, prior art generally recognized that Lpp-OmpA surface vehicle system as exemplified by Francisco et al may be used in other stain of bacterium including Salmonella (see page 516, Earhart C.F. Methods in Enzymology, 2000, 326, 506-516, IDS, cited in support of arguments without relying the reference for rejection). In view of foregoing it is apparent that one of ordinary skill was well aware of the required structures and method for displaying a functional scFv antibody fragment to the outer surface of another microorganism as evident from the teaching of Francisco. It would have been obvious to one of ordinary skill in the art to substitute *E.Coli* with another

microorganism such as attenuated strain of *Salmonella typhimurium* (VNP 200009 or SL7207) for displaying CEA scFv antibody on the surface of the microorganism as Wu taught required sequences of anti-CEA that would have resulted in stable dimers of anti-CEA scFv.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., to achieve cellular entry) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Additionally, it appears Applicant's arguments focus on each reference individually. However, the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. *In re Nilssen*, 7 USPQ2d 1500 (Fed. Cir. 1988). In the instant case, contrary to applicants' assertion that describes differences between intracellular (Salmonella) and extracellular bacterium (E.coli) (see page 6 of the argument), it is noted that the reference of Bermudes et al/ Szalay et al teach the intracellular bacterium Salmonella for specifically targeting tumor cells, while Francisco et al teach a method of displaying an antibody on the surface of the microorganism. Thus, applicants' assertion directed to distinguish cellular entry by two bacteria is not persuasive. It would have been obvious to one the artisan to express anti human CEA antibody or scFv antibody on the surface of genetically modified attenuated strain of microorganism disclosed by Bermudes et al/ Szalay using the method disclosed by Francisco et al to obtain microorganism that displays CEA or other antibody as disclosed in the

instant application. Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Earhart C.F. Methods in Enzymology, 2000, 326, 506-516, IDS.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANOOP SINGH whose telephone number is (571)272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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